Immune thrombocytopenic purpura (ITP) — adult

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Condition for which IVIg has an established therapeutic role.

Specific Conditions	• Newly Diagnosed Immune thrombocytopenic purpura (ITP) • Persistent Immune thrombocytopenic purpura (ITP) • Chronic Immune thrombocytopenic purpura (ITP) • Evans syndrome - with significant Immune thrombocytopenic purpura (ITP) - adult
Indication for IVIg Use	• Newly diagnosed ITP — initial Ig therapy • ITP in pregnancy — initial Ig therapy • ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage • Newly diagnosed or persistent ITP — subsequent therapy (diagnosis <12 months) • Refractory persistent or chronic ITP — splenectomy failed or contraindicated and second-line agent unsuccessful • Subsequent or ongoing treatment for ITP responders during pregnancy and the postpartum period • ITP and inadequate platelet count for planned surgery • HIV-associated ITP
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	Immune thrombocytopenic purpura (ITP) is a reduction in platelet count (thrombocytopenia) resulting from shortened platelet survival due to anti-platelet antibodies, reduced platelet production due to immune induced reduced megakaryopoeisis and/or immune mediated direct platelet lysis. When counts are very low (less than $30x10^9$/L), bleeding into the skin (purpura) and mucous membranes can occur. Bone marrow platelet production (megakaryopoiesis) is morphologically normal. In some cases, there is additional impairment of platelet function related to antibody binding to glycoproteins on the platelet surface. It is a common finding in patients with human immunodeficiency virus (HIV) disease, and while it may be found at any stage of the infection, its prevalence increases as HIV disease advances. Around 80 percent of adults with ITP have the chronic form of disease. The highest incidence of chronic ITP is in women aged 15 to 50 years, although some reports suggest increasing incidence with age. Chronic ITP may relapse and remit spontaneously and the course may be difficult to predict. If the platelet count can be maintained at a level that prevents spontaneous bleeding or bruising, the outlook is good. The terminology from the ITP International Consensus Report (Provan et al, 2010) for the phases and severity of ITP disease are used in these Criteria. Newly diagnosed is used for all cases within three months of diagnosis; Persistent ITP relates to patients not achieving spontaneous remission within 3 to 12 months from diagnosis or not maintaining a response to treatment during this time; chronic ITP indicates patients with ITP lasting greater than 12 months. Severe ITP relates to patients with clinically relevant bleeding mandating treatment or new

	bleeding mandating a change in therapy. In the context of these Criteria, refractory refers to patients where splenectomy has failed to correct the ITP or splenectomy is contraindicated and second line therapy has been unsuccessful. Evans syndrome is a rare but serious autoimmune disease defined by the simultaneous or sequential occurrence of autoimmune haemolytic anaemia (AIHA) and ITP without underlying aetiology. As such, it is a diagnosis of exclusion and other disorders, such as collagen vascular diseases, especially systemic lupus erythematosus (SLE) and scleroderma should be ruled out. The 2005 review by Norton and Roberts provided perspective on diagnosis, clinical features and management.
Justification for Evidence Category	Five small prospective studies, including three randomised studies, demonstrated equivalent efficacy of intravenous immunoglobulin (IVIg) in comparison to prednisone 1 mg/kg/day and high-dose dexamethasone regimen. Overall, the studies found a dose response with more rapid increment in platelet counts at scheduling greater than or equal to 0.8 g/kg on day one compared with 0.4 g/kg/day for three days. A small controlled study (10 patients in each arm) of HIV-positive patients with severe thrombocytopenia reported possible benefit for the restoration and maintenance of platelet count for the duration of the haemorrhagic disorder (Biotext 2004). An international consensus statement from January 2010 (Provan et al 2010) reported on new data and provided consensus-based recommendations relating to diagnosis and treatment of immune thrombocytopenic purpura (ITP) in adults, in children, and during pregnancy. This statement concluded that few randomised controlled trials (RCTs) have been conducted and that multi-centre, prospective RCTs are required. A 2005 review on the management of Evans syndrome, based on Massachusetts Hospital data and a literature review, showed a transient response in all patients unless IVIg was given every three weeks (Norton and Roberts 2006). The review concluded that the data supported a role for IVIg in first-line therapy. It was not clear whether it was important for steroids to be given at the same time, although this is common practice. A total dose of 2g/kg in divided doses appeared to be sufficient. The review also stated that there might be a role for IVIg in preference to steroids in the acute setting in very young children. A recent meta-analysis of low to medium quality evaluated outcomes of 13 small RCTs comparing high dose (2g/kg) to lower dose (1g/kg) IVIg in acute ITP. The analysis demonstrated equivalent efficacy for all endpoints studied including platelet responses and control of bleeding (Qin YH et al 2010) in both high dose and low dose groups.
Diagnosis Requirements	A diagnosis must be made by a Haematologist, Paediatrician or a General Medicine Physician.

Qualifying Criteria for IVIg Therapy

Newly diagnosed ITP — initial Ig therapy

This indication should be used to request one-off treatment in patients who have been diagnosed with ITP in the last three months.

For patients requiring subsequent or ongoing therapy, where the diagnosis was made in the last 3 to 12 months, use indication **Newly diagnosed or persistent ITP – subsequent therapy (diagnosis < 12 months).**

For refractory or chronic ITP patients use **indication Refractory persistent or chronic ITP – splenectomy failed or contraindicated and second-line agent unsuccessful.**

- Current platelet count is less than $30x10^9$/L

AND

- There is evidence of clinically significant bleeding

  OR
- There is a risk of clinically significant bleeding

AND

- No improvement in response to conventional doses of corticosteroid therapy for at least 14 days (unless a valid reason is provided)

  OR
- Corticosteroid therapy is contraindicated

ITP in pregnancy — initial Ig therapy

IVIg therapy is used to avoid corticosteroids, immunosuppressive agents and splenectomy during pregnancy. A total dose up to 2g/kg is available under this indication. If a response is achieved but not maintained with this initial Ig therapy, a subsequent induction dose prior to impending procedure or delivery or a maintenance dose titrated to maintain a platelet count above $30x10^9$/L may be administered every three to four weeks throughout pregnancy. To access the subsequent induction or maintenance dose use the indication –**Subsequent or ongoing treatment for ITP responders during pregnancy and the postpartum period**.

- Pregnant patient and current platelet count represents potential risk:
  - Less than $30x10^9$/L with risk of haemorrhage
  - Less than $80x10^9$/L with life-threatening haemorrhage
  - Less than $100x10^9$/L and impending delivery

ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage

- Life-threatening bleeding or the potential for life-threatening bleeding

AND

- Current platelet count is:
  - Less than 100 $x10^9$/L in patients with intracranial haemorrhage
  - Less than 50 $x10^9$/L in patients with life-threatening haemorrhage
  - Less than 30 $x10^9$/L in patients with a risk of haemorrhage

AND

- A rapid response is required

  OR

- Conventional dose of corticosteroids have failed to improve count (unless a valid reason is provided)

  OR

- Corticosteroid therapy is contraindicated

Newly diagnosed or persistent ITP — subsequent therapy (diagnosis <12 months)

This indication should be used to request maintenance therapy for patients who have been diagnosed within the past 12 months. Where the diagnosis was made greater than 12 months ago a request should be submitted using the indication **Refractory Persistent or Chronic ITP— splenectomy failed or contraindicated and second-line agent unsuccessful.**

- A diagnosis of ITP has been made within the last 12 months

  AND

- The current platelet count is less than $30x10^9/L$

AND

- There is evidence of clinically significant bleeding

  OR

- There is a risk of clinically significant bleeding

AND

- No improvement in response to conventional doses of corticosteroid therapy for at least 14 days (unless a valid reason is provided)

  OR

- Corticosteroid therapy is contraindicated

AND

- At least one second line agent has been unsuccessful in raising the platelet count above $30x10^9/L$

Review must be undertaken six monthly by a haematologist, paediatrician or general physician.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Ongoing use of IVIg should be primarily to prevent bleeding while other treatment options are explored, including splenectomy.

Refractory persistent or chronic ITP — splenectomy failed or contraindicated and second-line agent unsuccessful

This indication should be used to request maintenance therapy for patients where a diagnosis was made greater than 12 months ago. For patients who have been diagnosed within the past 12 months a request should be submitted using the indication **Newly diagnosed or persistent ITP – subsequent therapy (diagnosis < 12 months).**

- Date of initial ITP diagnosis is greater than 12 months in the past

  AND

- Current platelet count less than $30x10^9$/L in a patient with persistent or chronic ITP

AND

- There is clinically significant bleeding

  OR

- There is a risk of clinically significant bleeding

AND

- Previous Ig therapy resulted in a resolution of active bleeding or a reduction in evidence of bleeding, correlating with a doubling of baseline platelet count and/or an increase in platelet count increment of greater than $10x10^9$/L within seven days

  OR

- In patients without active bleeding, a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of previous Ig therapy

AND

- Splenectomy has failed to correct thrombocytopenia

  OR

- Splenectomy is contraindicated

AND

- Therapy with a second-line agent has been unsuccessful in raising the platelet count above $30x10^9$/L

With ongoing therapy, IVIg may be administered to achieve a platelet count of greater than $30x10^9$/L.

Review must be undertaken six monthly by a haematologist, paediatrician, or general physician.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Subsequent or ongoing treatment for ITP responders during pregnancy and the postpartum period

IVIg therapy is used to avoid corticosteroids, immunosuppressive agents and splenectomy during pregnancy. A dose up to 2g/kg is available under the **ITP in pregnancy - initial therapy** indication. If a response is achieved following this initial therapy but not maintained, a maintenance dose titrated to maintain a platelet count above $30x10^9$/L may be administered every three to four weeks throughout pregnancy under this indication. A subsequent one-off induction dose of up to 2g/kg prior to impending procedure or delivery is also available under this indication.

- Pregnant patient and current platelet count represents potential risk:
  - Less than $30x10^9$/L and risk of haemorrhage
  - Less than $80x10^9$/L and life-threatening haemorrhage
  - Less than $100x10^9$/L and impending delivery

AND

- Previous Ig therapy resulted in resolution of active bleeding or a reduction in evidence of bleeding, correlating with a doubling of baseline platelet count or an increase in platelet count by an increment of greater than $10x10^9$/L within seven days of Ig therapy

  OR

- In patients without active bleeding, the most recent Ig therapy resulted in a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L within seven days of therapy

ITP and inadequate platelet count for planned surgery

IVIg may be used to achieve a platelet count considered safe for surgery. The safe threshold will vary with the nature of the surgery and whether there is a concurrent bleeding risk. Recommended platelet counts for patients without concurrent risks of bleeding:

- minor dental work (greater than $30x10^9$/L)
- major dental work (greater than $50x10^9$/L)
- minor surgery (greater than $50x10^9$/L)
- major surgery (greater than $80x10^9$/L)
- major neurosurgery (greater than $100x10^9$/L)

- Surgery is planned

AND

- Platelet count is below the accepted cut-off for the intended surgery

	HIV-associated ITP • Failure of antiretroviral therapy with intracranial haemorrhage and platelet count less than $80x10^9$/L OR • Failure of antiretroviral therapy and other life-threatening haemorrhage with a platelet count of less than $50x10^9$/L OR • Failure of antiretroviral therapy and risk of clinically significant bleeding and platelet count less than $30x10^9$/L
Exclusion Criteria	Evans syndrome – where predominant feature is AIHA - see Autoimmune haemolytic anaemia (AIHA)
Review Criteria for Assessing the Effectiveness of IVIg Use	Newly diagnosed ITP — initial Ig therapy **Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Resolution of active bleeding, or a reduction in evidence of bleeding correlating with a doubling of platelet count or an increment in platelet count greater than $10x10^9$/L within seven days. OR • In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of Ig therapy ITP in pregnancy — initial Ig therapy **Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Resolution of active bleeding, or a reduction in evidence of bleeding correlating with a doubling of platelet count or an increment in platelet count greater than $10x10^9$/L within seven days OR • In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of Ig therapy

ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage

Review Is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.

- Resolution of, or a reduction in evidence of bleeding correlating with a doubling of platelet count or an increment in platelet count greater than $10x10^9$/L within seven days of Ig therapy

  OR

- In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count of greater than $30x10^9$/L was demonstrated within seven days of Ig therapy

Newly diagnosed or persistent ITP — subsequent therapy (diagnosis <12 months)

Review must be undertaken six monthly by a haematologist, paediatrician or general physician.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Ongoing use of IVIg should be primarily to prevent bleeding while other treatment options are explored, including splenectomy.

On review of the initial authorisation period

- Current platelet count is less than $30x10^9$/L

AND

- Ig therapy resulted in a resolution of active bleeding or a reduction in evidence of bleeding correlating with a doubling of baseline platelet count or an increment in platelet count of greater than $10x10^9$/L within seven days of Ig therapy

  OR

- In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of Ig therapy

On review of a continuing authorisation period

- Current platelet count is less than $30x10^9$/L

AND

- Ig therapy resulted in resolution of active bleeding or a reduction in evidence of bleeding, correlating with a doubling of baseline platelet count or an increment in platelet count of greater than $10x10^9$/L within seven days of Ig therapy

  OR

- In patients without active bleeding, a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of previous Ig therapy

Refractory persistent or chronic ITP — splenectomy failed or contraindicated and second-line agent unsuccessful

Review must be undertaken six monthly by a haematologist, paediatrician or general physician.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

On review of the initial authorisation period

- The platelet count responds to Ig therapy but cannot be maintained above $30x10^9$/L

AND

- Ig therapy resulted in resolution of active bleeding or a reduction in evidence of bleeding, correlating with a doubling of baseline platelet count or an increase in platelet count by an increment of greater than $10x10^9$/L within seven days of Ig therapy

  OR

- In patients without active bleeding, a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of the most recent Ig therapy

On review of a continuing authorisation period

- The platelet count responds to Ig therapy but cannot be maintained above $30x10^9$/L

AND

- Ig therapy resulted in resolution of active bleeding or a reduction in evidence of bleeding, correlating with a doubling of baseline platelet count or an increase in platelet count by increment of greater than $10x10^9$/L within seven days of Ig therapy

  OR

- In patients without active bleeding, a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of previous Ig therapy

The objective of therapy is to maintain a safe platelet count while other treatment options are explored.

Subsequent or ongoing treatment for ITP responders during pregnancy and the postpartum period

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.

- Resolution of, or a reduction in evidence of bleeding correlating with a doubling of platelet count or increase in platelet count by an increment greater than $10x10^9$/L within seven days

  OR

- In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of previous Ig therapy

ITP and inadequate platelet count for planned surgery

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.

- Platelet count is above the accepted cut-off for the intended surgery for patients without concurrent risk factors

  OR

- Platelet count is above the accepted cut-off for the intended surgery for patients with concurrent risk factors

HIV-associated ITP

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.

- Resolution of, or a reduction in evidence of bleeding correlating with a doubling of platelet count or in platelet count of greater than $10x10^9$/L within seven days of Ig therapy

  OR

- In patients without active bleeding a doubling of baseline platelet count and a rise in platelet count to greater than $30x10^9$/L was demonstrated within seven days of Ig therapy

Dose

Newly diagnosed ITP — initial Ig therapy

- **Initial Dose** - 0.8–2g/kg as a single or divided dose

The objective of IVIg therapy in ITP is to maintain a safe platelet count while other therapeutic options are explored.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

ITP in pregnancy — initial Ig therapy

- **Induction Dose** - 0.8–2 g/kg as a single dose or divided dose.
  A total dose up to 2g/kg is available under this indication. If a response is achieved but not maintained with this initial Ig therapy, a subsequent induction dose prior to impending procedure or delivery or a maintenance dose titrated to maintain a platelet count above $30x10^9$/L may be administered every three to four weeks throughout pregnancy. To access the subsequent induction or maintenance dose use the indication – **Subsequent or ongoing treatment for ITP responders during pregnancy and the postpartum period**.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administartion and contraindications.

ITP with life-threatening haemorrhage or the potential for life-threatening haemorrhage

- **Induction Dose** - 1–2g/kg as a single dose or divided dose

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Newly diagnosed or persistent ITP — subsequent therapy (diagnosis <12 months)

- **Maintenance Dose** - 0.4–2g/kg in a single or divided dose at 4 to 6 weekly intervals titrated to symptoms and platelet count up to a maximum of 2g/kg/4 week period.

The objective of IVIg therapy in ITP is to maintain a safe platelet count while other therapeutic options are explored.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindication.

Refractory persistent or chronic ITP — splenectomy failed or contraindicated and second-line agent unsuccessful

- **Maintenance Dose** - 0.4–2g/kg in a single or divided dose at 4 to 6-weekly intervals titrated to symptoms and platelet count up to a maximum of 2g/kg/4 week period.

The objective of IVIg therapy in ITP is to maintain a safe platelet count while other therapeutic options are explored.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Subsequent or ongoing treatment for ITP responders during pregnancy and the postpartum period

- **Maintenance Dose** - 0.4–2g/kg in single or divided dose at 4- to 6-weekly intervals titrated to symptoms and platelet count up to a maximum of 2g/kg/4 week period.

  The frequency and dose should be titrated to maintain a platelet count of at least $30x10^9$/L.

- **Induction dose prior to impending procedure or delivery** - 0.8 to 2g/kg in single or divided dose

  In rare circumstances a second induction dose of up to 2g/kg may be required (e.g. where the procedure was postponed/rescheduled after the initial induction dose). A second dose of up to 2g/kg will only be approved if a response to the initial induction dose was achieved.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindication.

ITP and inadequate platelet count for planned surgery

- **Induction Dose** - 1–2 g/kg as a single or divided dose

While a dose of 1-2g/kg is suggested, a lower dose may be appropriate if the patient has previously responded to a lower dose.

IVIg may be used to achieve a platelet count considered safe for surgery.

The safe threshold will vary with the nature of the surgery. If an additional induction dose is required prior to a surgical procedure where there has been a response to IVIg, but the platelet count falls to below safe levels for that procedure, a new application is required.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration, and contraindications.

HIV-associated ITP

- **Induction Dose** - 1–2 g/kg as a single dose or divided dose

The objective of IVIg therapy in ITP is to maintain a safe platelet count while other therapeutic options are explored.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administartion and contraindications.

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